MANAGEMENT OF NODULAR THYROID DISEASES

Dr Loh Keh Chuan

INTRODUCTION

The term nodular thyroid disease encompasses subjects with single or multiple, palpable or non-palpable thyroid nodules. Evaluation is necessary in patients with nodular goitre to exclude the possibility of malignancy, toxicity and/or local compressive symptoms. This article focuses on the practical aspects of the management of nodular thyroid disease for the family physician. Although the approach to patients with a solitary thyroid nodule and that for patients with a non-toxic goitre are discussed separately, one should appreciate that there is significant overlap in the pathogenesis, aetiology, clinical significance, evaluation and management of both entities. The article concludes with a brief overview on the management of patients with differentiated thyroid cancer.

APPROACH TO A SOLITARY THYROID NODULE

The lifetime risk for developing a nodule is estimated between 4% to 7% in the general population. The frequency of palpable thyroid nodules – about half of which are single on physical examination – increases throughout life. Gender wise, thyroid nodules are about four times more common in women than in men. In autopsy series however, about half of the thyroids in adults have one or more nodules, the majority of which are subcentimeter in size. These findings are corroborated by the use of ultrasonography, with 40% to 50% of the thyroids in the population found to have incidentally detected nodules, so called thyroid incidentalomas.

The majority (95%) of thyroid nodules are benign with the aetiology presented in Box 1. As malignancy occurs in only 1 in 20 thyroid nodules, identifying thyroid cancer remains challenging because thyroid nodules are so common. The causes of malignant thyroid nodules are summarised in Box 2. Box 3 summarises the factors suggesting the diagnosis for thyroid cancer in patients with thyroid nodules.

Box 1. Causes of Benign Nodules

- Simple or complex cyst
- Hyperplastic or colloid nodule
- Lymphocytic thyroiditis
- Granulomatous thyroiditis
- Follicular cell or Hurthle cell adenoma

LOH KEH CHUAN, Consultant Endocrinologist, Department of General Medicine, Tan Tock Seng Hospital

Box 2. Causes of Malignant Nodules

- Primary thyroid cancer
  - Follicular-cell derived:
    - Papillary thyroid cancer
    - Follicular thyroid cancer
    - Hurthle cell thyroid cancer
  - Medullary thyroid cancer
  - Anaplastic thyroid cancer
  - Thyroid lymphoma
- Metastatic cancer

Box 3. Risk Factors for Diagnosis of Thyroid Cancer in Patients with Solitary Thyroid Nodules

Extremes of age: I 20 yrs or L 60 yrs
Male gender
Childhood history of head and neck irradiation
Rapid growth (esp. if during T4 therapy)
Neck discomfort, pain or compression symptoms
Firm texture, immobility, large size
Lymphadenopathy
Family history of thyroid cancer

Role of Fine Needle Aspiration Cytology (FNAC)

Fine needle aspiration cytology (FNAC) is now universally accepted as the first step in the evaluation of patients with thyroid nodule. In experienced hands, FNAC provides a diagnostic accuracy of 95% with specificity and sensitivity rates of 92% and 83% respectively. The corresponding false negative and false positive results are low, being less than 5% and 3% respectively.

FNAC may yield one of the four results (Fig. 1): benign (65-75%), malignant (5%), follicular neoplasm (15-20%), or insufficient material (10-15%). FNAC is reliable in identifying papillary thyroid cancer, which constitutes 90% of differentiated follicular-cell derived thyroid cancer. However, the cytology obtained from FNAC of a follicular thyroid cancer may be identical to that obtained from a follicular adenoma, and the diagnosis of malignancy is based on the presence of capsular or vascular invasion on histological examination of the surgical specimen.

The management strategy may be summarised as follows (Fig. 1): if the lesion is benign, the patient may be put on levo-thyroxine (T_4) therapy to suppress thyroid stimulating hormone (TSH) to a level just below normal, or the patient may simply be followed for evidence of growth or obstructive symptoms. If the lesion is malignant, the patient is referred for surgery. If the finding is suspicious for follicular or Hurthle cell neoplasm, lobectomy is usually indicated to exclude malignancy which may be found in 15-20% of such nodules. A repeat FNAC is

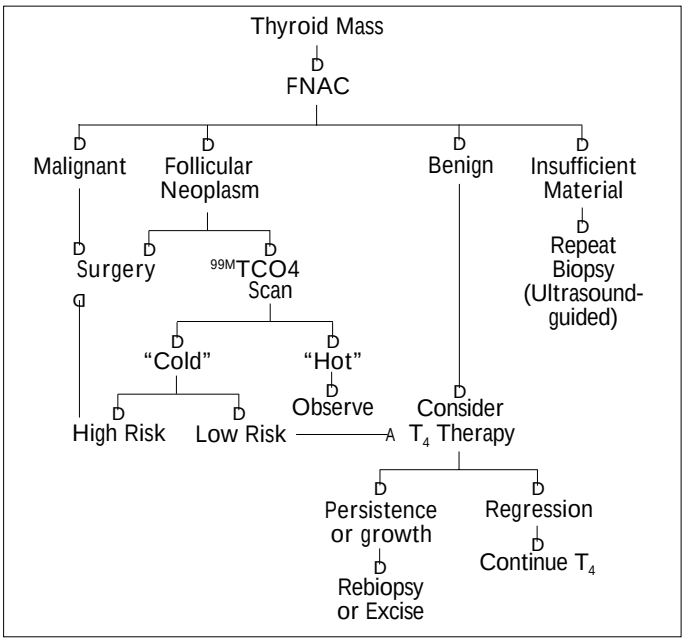

Fig. 1. Algorithm for clinical approach to thyroid nodule.

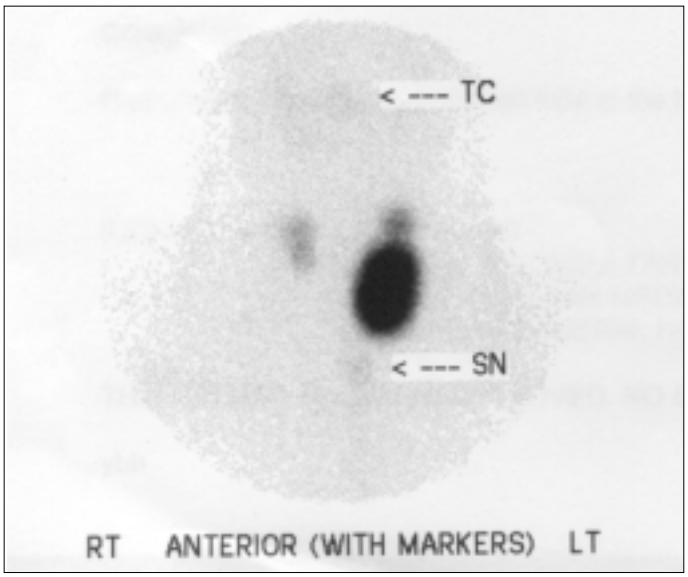

Fig. 2. Tc-99m pertechnetate thyroid scan showing a "hot" nodule in the left thyroid lobe and suppressed tracer uptake in the rest of the thyroid gland, providing reassurance that the nodule is most likely benign. Thyroid radionuclide scan was performed because FNAC of the solitary left thyroid nodule revealed a follicular neoplasm and patient was not keen for surgery.

necessary if there is insufficient material for diagnosis, and the use of thyroid ultrasonography may improve the yield for deep-seated or mixed cystic nodules.

This approach eliminates unnecessary biochemical tests and radionuclide imaging in the initial evaluation because most patients with a thyroid nodule have normal serum TSH concentrations and hypofunctioning (i.e. cold) nodule. Conversely, serum TSH and a radionuclide scan may be useful to determine the functional status of a nodule in patients who are reluctant to undergo surgery despite the suggestion of a follicular neoplasm on FNAC. This is because the finding of a functioning (i.e. hot or warm) nodule provides reassurance that the lesion is almost always benign (Fig. 2).

In summary, evaluation of a patient with thyroid nodule can be expensive, considering the many biochemical and imaging tools available. FNAC is now regarded as the most cost-effective method of evaluation for thyroid nodule. Importantly, this has resulted in a significant decrease in the number of patients who are being operated upon for benign nodular goitre and the increased detection rate of thyroid cancer amongst those who are being referred for surgery as compared to the pre-FNAC era.

Ultrasound-guided management of thyroid nodule

Recent technical advances such as grey-scale imaging, real-time sonography and the use of high resolution probes and linear phased-array transducers have made ultrasound a more useful diagnostic tool to the clinician. This is particularly useful for thyroid disease management, especially when the endocrinologist or thyroidologist performs "hands on" real-time ultrasound as part of the physical examination. Equipped with history, physical examination and laboratory data, the clinician is able to accrue much more valuable information from real-time ultrasound examination by anticipating what pathology might be present and knowing what to look for.

One of the primary uses for thyroid ultrasound is the evaluation and follow-up of thyroid nodules. The reduced cost of ultrasound machine now allows thyroidologist to perform ultrasound in the clinic and avoid any delay in referring patients to the radiology clinic. Performing ultrasound at the time of FNAC offers certain definite advantages. Visualisation of the nodule at the time of FNAC allows for better selection of needle size and needle length. Ultrasound may also reveal other unsuspected nodules and allow FNAC of the dominant or suspicious nodules (Fig. 3). More importantly, ultrasound at the time of FNAC helps select nodules that should be biopsied under ultrasound-guidance (eg. mixed cystic nodules), thus decreasing the number of inadequate cytology specimens.

Role of thyroid hormone suppression therapy

Because TSH is believed to be one of the many factors responsible for pathological thyroid growth, thyroid hormone suppressive therapy has been used for many years in an attempt to reduce the size of thyroid lesions. Typically, the patient is given a 6-12 month trial of levo-thyroxine at a dose titrated to result in TSH suppression to below the lower limit of normal (0.1-0.3 mIU/L) using a sensitive TSH assay. Growth of a nodule or lack of reduction in size during therapy raises suspicion of malignancy.

Data on suppression trials however showed that less than a third of nodules shrink in response to suppression therapy. Routine thyroid hormone suppression therapy is therefore no longer recommended, especially if the nodules are L 3 cm in size or if the baseline TSH levels are already low. Furthermore, there is also concern with potential adverse effects of osteopenia and altered cardiac function after long-term suppressive doses of T_4.

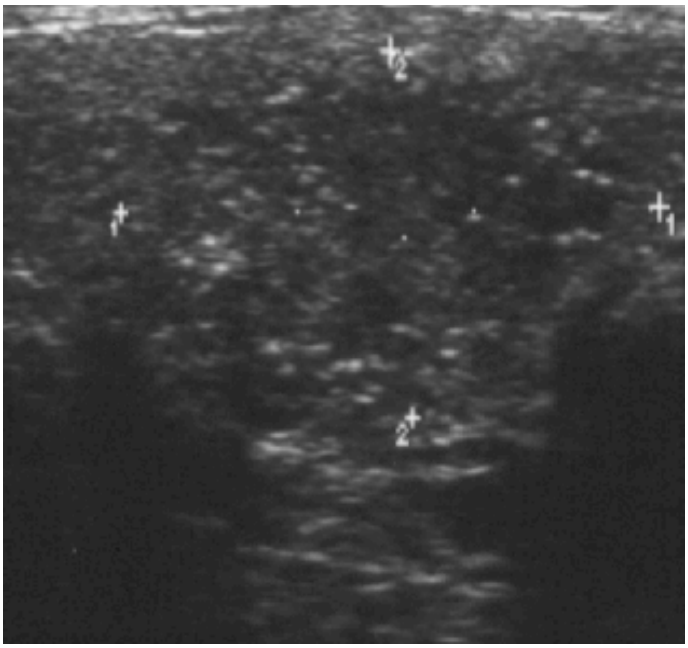

Fig. 3. Thyroid ultrasound showing a solid hypoechoic nodule with microcalcifications (features suspicious of malignancy). FNAC revealed papillary thyroid cancer which was histologically confirmed post thyroidectomy.

APPROACH TO A NON-TOXIC GOITRE

The common causes of non-toxic diffuse or nodular goitre are listed in Box 4. Whilst iodine deficiency is the most common cause of goitre world-wide, chronic lymphocytic (or autoimmune) thyroiditis and genetic predisposition for goitrogenesis are probably the two commonest causes of euthyroid goitre in iodine-replete regions like Singapore. A family history of goitre is often found in subjects with euthyroid goitre. These individuals are likely to have partial enzymatic disorders responsible for thyroid hormone biosynthesis, which result in compensatory glandular hypertrophy and hyperplasia to maintain euthyroidism. Diffuse goitres tend not only to grow with time but also become nodular. Nodule formation is believed to result from constitutive heterogeneity of the growth responses of individual thyroid follicular cells to thyroid growth-stimulatory factors. Most thyroid follicular cells replicate only when TSH is present. However, the amount of TSH needed for replication varies among cells. A few cells may have the capacity to replicate autonomously, even in the absence of TSH. Therefore, diffuse goitre assumes multinodularity with time characterised clinically by thyroid growth and nodule formation.

Box 4. Causes of Non-toxic Goitre (diffuse or nodular)

- Chronic lymphocytic thyroiditis (Hashimoto's disease)
- Sporadic or familial goitre
  (includes inherited disorders of thyroid hormone biosynthesis)
- Neoplasms: benign or malignant
- Acromegaly*
- Drugs: eg. lithium, perchlorate**

* Up to 40% of patients with acromegaly may have goitre

** Both drugs often produce hypothyroid goitre

Nontoxic goitres usually grow slowly over decades, and many of them never cause any problems. However, patients with large goitre and particularly those with substernal extension may eventually develop compressive symptoms like inspiratory stridor and dysphagia. Over time, multinodular goitre may also develop functional autonomy and evolve into a toxic nodular goitre. This is because not only the growth potential but also the functional activity of the individual thyroid follicular cell varies widely in the multinodular goitre. Activating mutations in the TSH receptor may account for some autonomously functioning thyroid adenomas and hyperfunctioning nodules of toxic multinodular goitres.

Evaluation and Treatment Options

Patients with any nodule that is palpably prominent or rapidly growing in a multinodular goitre should be evaluated for malignancy in a similar fashion as the approach to a solitary thyroid nodule (Fig. 1). Thyroidectomy is the treatment for patients with suspicion of malignancy or compressive symptoms.

In asymptomatic patients with diffuse nontoxic goitre, T_4 therapy in an attempt to suppress TSH to the low normal range (0.1-0.3 mU/L) may be effective in reducing the thyroid volume or preventing its further growth. However, T_4 suppressive therapy is unlikely to benefit older patients with large multinodular goitres or glands that developed functional autonomy. In elderly patients with high operative risk or who refuse surgery, 131-iodine therapy may be used to reduce goitre size and relieve compressive symptoms.

Periodic thyroid function testing should be performed in patients with long-standing multinodular goitre to detect evolution into toxic nodular stage. Depending on the size of the goitre and the presence of associated symptoms, the patients may be treated medically with thionamides or definitively by 131-iodine or surgery. Conversely, periodic thyroid function testing may help to detect hypothyroidism early in patients with autoimmune thyroiditis characterised by the presence of euthyroid goitre and positive thyroid autoantibodies.

MANAGEMENT OF DIFFERENTIATED THYROID CANCER

Differentiated thyroid cancers of follicular cell origin (i.e. papillary and follicular thyroid cancers) constitute the most common endocrine neoplasms. Despite the slow progression and good prognosis of the disease, differentiated thyroid cancers kill more patients than all other endocrine malignancies combined. Most thyroid cancers present as asymptomatic thyroid nodules, of which 80% to 95% are benign hyperplastic nodules rather than true neoplasms. Over the last decade, FNAC of thyroid nodule has proven to be the most effective way to diagnose thyroid cancer and to select patients with suspicious nodule for surgery.

The guiding principle in managing patients with differentiated thyroid cancer is to avoid either overaggressive treatment in a patient with an excellent prognosis, or inadequate therapy for the unusual patient with a high risk of tumour

recurrence and possible death from thyroid cancer. However, what constitutes the appropriate therapy in patients with differentiated thyroid cancer is still a subject of intense debate amongst the experts because no prospective randomised clinical trials exist.

Despite on-going debate on the appropriate treatment strategies for differentiated thyroid cancer, careful analysis of patients treated by well-defined methods now gradually prove the benefit of more aggressive initial tumour management. There is now a greater consensus among experts to treat most differentiated thyroid cancer patients, except for those in the very low-risk category, with total or near-total thyroidectomy and postoperative 131-iodine ablation of residual thyroid tissue, followed by long-term T_4 suppression of serum TSH concentrations. The treatment approach is multi-disciplinary and best co-ordinated by the endocrinologist.

Because of the risks of recurrence even several decades later, patients who survived differentiated thyroid cancer should have long-term T_4 suppression therapy and follow-up. Periodic 131-iodine whole body scan, serum thyroglobulin monitoring and neck ultrasound examination are some of the useful tools for tumour surveillance. As data derived from controlled trials are unlikely to be available in the near future, management of patients with differentiated thyroid cancer remains individually tailored with clinical decisions based on balancing the potential benefit and morbidity of any treatment modality.

SUGGESTED READINGS

1. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med 1993; 328:553-9.
2. Ortiz R, Hupart KH, DeFesi CR, Surks MI. Effect of early referral to an endocrinologist on efficiency and cost of evaluation and development of treatment plan in patients with thyroid nodules. J Clin Endocrinol Metab 1998; 83:3803-7.
3. Khurana K, Richards V, Chopra P, et al. The role of ultrasonography-guided fine-needle aspiration in the management of palpable and non-palpable thyroid nodules. Thyroid 1998; 8:511-5.
4. Marqusee E, Benson CB, Frates MC et al. Usefulness of ultrasonography in the management of nodular thyroid disease. Ann Intern Med 2000; 133:696-700.
5. Oertel YC. Fine-needle aspiration and the diagnosis of thyroid cancer. Endo Metab Clin N Amer 1996; 25:69-92.
6. Loh KC, Greenspan FS, Gee L, Miller TR, Yeo PPB. pTNM classification for papillary and follicular thyroid carcinomas: A retrospective analysis of 700 patients. J Clin Endocrinol Metab 1997; 82:3553-62.